

REMARKS

Claims 1-3, 5-7 and 9-11 are all the claims pending in the application.

Preliminary Matter

1. At page 1 of the Advisory Action, the Office fails to acknowledge receipt of the Notice of Appeal filed on May 26, 2009. Applicants respectfully request that the Examiner acknowledge receipt of the Notice of Appeal in the next action.

2. At page 2 of the Advisory Action, the Office states that the IDS filed on April 13, 2009 was not considered, but the Examiner does not explain why it was not considered. The IDS met all the requirements of 37 CFR § 1.97(d) in that it was accompanied by a statement under 37 CFR § 1.97(e) and the fee set forth in 37 CFR § 1.17(p).

Accordingly, the Examiner is requested to review the cited references and return a signed copy of the PTO Form SB/08.

Claims 1-3, 5-7 and 9-11 Define Allowable Subject Matter

1. Claims 1-3, 5, 6 and 9-11 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Goodwin *et al.* (U.S. Patent No. 5,496,722; “Goodwin #1”), Baker *et al.* (In Vitro. Cell Dev. Biol., vol 33, page 358, 1997; “Goodwin #2”), Goodwin *et al.* (In Vitro. Cell Dev. Biol., vol 33, page 366, 1997; “Goodwin #3”) and Schwarz *et al.* (USP 5,026,650; “Schwarz”) in view of Unsworth *et al.* (Nature Medicine; “Unsworth”), Wikipedia, Bock *et al.* (Tissue Engineering of Cartilage and Bone; “Bock”) and Bartlett (Ovarian Cancer Methods and Protocols).

At pages 2-3 of the Advisory Action, the Office asserts that Applicants' traversal arguments presented in the Response filed April 24, 2009 are not persuasive for the reasons outlined below. Applicants submit the following response to each and every point that the Examiner raises in the Advisory Action as follows.

a) The Office states that the additional references submitted to show that MSCs are an exception to the general protocol for mammalian cells taught by Current Protocols in Cell Biology was not considered because Applicants did not provide a reason why this evidence was not previously submitted and because it seems to contradict the Applicants' previous assertion that cells in general are not cultured to confluence. The arguments directed toward this evidence also were not considered, in view of the apparent contradiction.

Initially, Applicants submit that there was an inadvertent clerical error in the previous Response to the Office Action filed July 28, 2009. Specifically, the third paragraph at page 6 of the Response to the Office Action filed July 28, 2009 should have read,

Moreover, the confluent 2D culture prior to subculturing is out of the common general knowledge in the field of mesenchymal stem cell culture. A person skilled in the art normally subcultures the cells when the cells grow to 70 to 90% confluency. It is known in the art that, if the cells are cultured to 100% confluency, then the proliferation property of the cells may be affected or the phenotype of the cells may alter due to contact inhibition. Thus, it is atypical to conduct the confluent 2D culture prior to subculturing.

Response to the Office Action, July 28, 2009.

In view of this clarification, Applicants respectfully submit that the additional art indicating that MSCs are an exception to the general protocol for mammalian cells taught by Current Protocols in Cell Biology is not contradictory to the Applicants' previous position that mesenchymal stem cells are not cultured to confluence in general.

Furthermore, Applicants again request that the Office consider the additional evidence of Majumdar *et al.* (*Journal of Cellular Physiology*, Column 17, Issue 1, Pages 57-66), Metzger (*Humana Press*, 2003, page 77) and Alhadlaq *et al.* (*J Dent Res*, 82(12): 951-956, 2003) submitted along with the Response to the Office Action filed April 24, 2009. The three cited references in support of Applicants' remarks of April 24, 2009 were submitted as evidence directed to an issue raised in the Examiner's Office Action of November 24, 2008. M.P.E.P § 609.05(c) states, "[t]o the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 CFR 1.97 and 37 CFR 1.98 in order to have the examiner consider the information contained in the document relied on by applicant." The references are timely submitted. Accordingly, the Examiner should consider them.

In view of the teachings of the above references, Applicants respectfully submit that one of ordinary skill in the art would have no reasonable expectation of success in differentiating mesenchymal stem cells to form cartilage tissue by using a confluent 2D culture prior to differentiation.

The M.P.E.P. § 2143.02 states, "[r]easonable [e]xpectation of [s]uccess [i]s [r]equired. ... [o]bviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); *In re O'Farrell*, 853 F.2d

894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). The references establish that there was no reasonable expectation for one of ordinary skill in the art in differentiating mesenchymal stem cells to form cartilage tissue by using a confluent 2D culture prior to differentiation.

Accordingly, Applicants respectfully submit that the presently claimed invention is not obvious in view of the cited references and request that the above obviousness rejection be reconsidered and withdrawn.

b) Regarding Applicants' previous arguments that no reason to combine the elements in the cited references has been identified, the Office states that this argument was "addressed on page 4 of the Final Office Action (11/24/08)." The Office previously stated that Goodwin #1 discloses promoting differentiation of mesenchymal stem cells to form cartilage tissue by producing cartilage tissue expressing Type II collagen from bone marrow mesenchymal cells. Page 4 of *the Final Office Action, November 24, 2008*. In reply, Applicants previously pointed out that the confluent culture technique for mesenchymal stem cells prior to their differentiation is not suggested by Goodwin #1. Therefore, there is no reason for one of ordinary skill in the art to modify Goodwin's mesenchymal stem cell culture technique to incorporate the confluent culture techniques to expand chondrocytes or ovarian tumor cells as recited in the present claims. *Response to the Office Action, April 24, 2009*.

As the Supreme Court recently stated, the "apparent reason to combine the known elements in a fashion claimed by the [claims] at issue ... should be made explicit." *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 slip op. at 14 (U.S. Apr. 30, 2007). In the present case, rather than indicating why one of skill in the art would choose to combine the references in a method

for cell differentiation, the Office is silent. Accordingly, Applicants respectfully request that the above obviousness rejection be reconsidered and withdrawn

c) The Office states that the argument that the Goodwin #1, #2, #3 references do not teach the 2D to 3D culture as a single element was not considered since the claims do not contain this limitation.

In response, Applicants respectfully point out that present independent claim 1 does recite the step of “(b) subculturing the cells from the confluent two-dimensional culture to three-dimensional culture” and thus the present claims indeed contain the limitation of the 2D to 3D culture. Furthermore, Applicants amended claim 1 specifically to clarify the step of “the subculture from confluent 2D culture to 3D culture” as discussed at page 4 of the Response to the Office Action, July 28, 2009.

As discussed at pages 5-6 of the Response to the Office Action filed April 24, 2009, Applicants respectfully submit that the combination of cited references fails to teach or suggest all the claim limitations of the invention, either explicitly or inherently. *Response to the Office Action, April 24, 2009*. In particular, these references do not expressly or inherently teach “subculturing the cells from confluent two-dimensional culture to three-dimensional culture.”

To establish *prima facie* obviousness of a claimed invention, all the cited references must recite all the claim limitations. *In re Royka*, 490 F.2d 981, 984 (CCPA 1974). For the reasons presented above, these references do not support a *prima facie* case of obviousness, and Applicants respectfully request that the above obviousness rejection be reconsidered and withdrawn.

d) The argument that the Applicants' method is superior to that disclosed by Goodwin #1, #2 and #3 was not considered because the current claims do not recite the limitation of lacking a carrier.

Applicants respectfully point out that the Office improperly disregards the argument that the claimed method is superior to that disclosed by Goodwin #1, #2 and #3 as submitted in the Response to the Office Action filed April 24, 2009.

Although the result of not requiring a carrier for the 3D mesenchymal stem cell culture is not explicitly disclosed in the specification or claims, as M.P.E.P. 716.02(f) states, "evidence and arguments directed to advantages not disclosed in the specification cannot be disregarded. *See In re Chu*, 66 F.3d 292, 298-99, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995)."

Accordingly, Applicants respectfully request that the Office consider the unexpectedly superior result of the presently claimed invention. As discussed at pages 6-7 of the Response to the Office Action filed April 24, 2009, while all 3D cultures disclosed by Goodwin #1, #2, and #3 require the use of Cytodex-3 microcarrier, the present invention does not require such a carrier in the 3D culture to form a desired tissue. *See* Columns 12, last paragraph, of Goodwin #1, Materials and Method section of Goodwin #2 and #3, and Example 1 of the present specification.

M.P.E.P. § 716.02(a) states, the "[p]resence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)." Thus, Applicants respectfully submit that the presently claimed invention is not obvious over the cited

references at least because of its unexpectedly superior result. Thus, Applicants respectfully request that the above obviousness rejection be reconsidered and withdrawn.

2. Claims 1-3, 5-7 and 9-11 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Goodwin #1, #2, #3 and Schwarz, and further in view of Yan *et al.* (US 2002/0168763; “Yan”) and Simpson *et al.* (US 2002/0090725; “Simpson”). The Examiner relies on Goodwin #1, #2, #3 and Schwarz to reject Claims 1-3, 5, 6 and 9-11 as described above and further rejects Claim 7 in view of Yan and Schwarz.

Previously, at page 8 of Applicants’ Response filed April 24, 2009, Applicants asserted that dependent Claim 7 should be allowable at least because the combination of the cited references fails to teach or suggest making cartilage tissue by adding dexamethasone as recited in Claim 7. *Response to the Office Action, April 24, 2009.*

However, the Office fails to address this argument in the Advisory Action. Applicants respectfully request again that the above obviousness rejection to claim 7 be reconsidered and withdrawn in view of the above remarks.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

RESPONSE UNDER 37 C.F.R. § 1.114(c)
U.S. Application No.: 10/581,911

Attorney Docket No.: Q95279

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

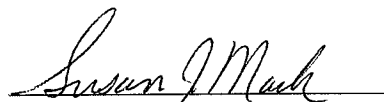
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